

Survival and failure outcomes in locally advanced esthesioneuroblastoma: a single centre experience of 15 patients

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Abstract Esthesioneuroblastoma (ENB) constitutes 3 % of all malignant intranasal tumors. As the tumor is very rare, the number of patients of ENB treated in individual departments is small. We present our institute's experience in combined modality management of 15 successive patients of ENB treated from 2006 to 2010. Clinical characteristics and treatment modality in form of surgery, radiotherapy and chemotherapy were noted. Kadish stage C was the most common stage (12 patients) followed by stage B (3 patients). Fourteen patients underwent primary surgery, of which nine had total excision and five had subtotal excision. One patient was treated with combination of

chemotherapy (CT) and radiotherapy (RT). Median RT dose delivered was 54 Gy. Twelve patients received CT with cisplatin and etoposide. Overall, eight patients had complete response, five had partial response, while one had static disease and progressive disease each. Two patients had distant metastases. Four-year loco-regional control (LRC) was 25 % and 4-year overall survival (OS) was 45 %. Most common presentation in our series was locally advanced tumors. Most of these patients require adjuvant RT, which helps in significant LRC. Systemic CT benefits in inoperable, advanced and high risk tumors. Risk-adapted and multimodality approach is the need of hour to achieve good control rates while minimizing treatment related toxicity.

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Introduction

Esthesioneuroblastoma (ENB) is a rare and uncommon tumor arising from the olfactory neuroepithelium, including the superior one-third of the nasal septum, cribriform plate, and superior turbinates, extending to base of the skull and to the intracranial space [1, 2]. It constitutes only 3 % of all intranasal neoplasms and its etiology remains unclear [3]. ENB can be seen in all ages, with peaks in the second and sixth decades of life [4]. Initial symptoms are non-specific and include nasal obstruction, epistaxis, hyposmia, exophthalmos and headache in correlation to the tumor extension. Evidence in the literature comes mainly from retrospective studies carried out over long periods in which diagnostic workup changed dramatically and therapeutic modalities in form of surgical techniques, radiotherapy

(RT) techniques and chemotherapy (CT) regimens have also evolved significantly [5–7]. On the basis of current evidence, a combined otolaryngologic and neurosurgical anterior craniofacial resection followed by postoperative RT is the main treatment modality in patients with localized ENB [8–10]. The role of chemotherapy in the treatment of ENB is controversial [11–15]. We herein report our institutional experience of 15 successive patients of ENB being treated from 2006 to 2010.

Materials and methods

Patient population and initial evaluation

We retrospectively reviewed the patients of ENB from November 2004 to November 2010 treated in our institute. Total number of patients was 15. We reviewed the records of these patients to extract the following information: age, sex, Karnofsky performance scale (KPS), clinical symptoms, histology, radiology (CT/MRI), Kadish stage, tumor extent, extent of surgical resection, surgical margins, radiation (technique, total dose, dose per fraction, number of fractions), chemotherapy (regimen, number of cycles), toxicity, response, recurrence, progression, metastases and death. Metastatic workup for distant metastases, including CECT of the chest, liver ultrasound, and/or bone scintigraphy was only performed if clinically indicated. Laboratory studies included blood chemistry (electrolytes, liver and kidney function tests), and a complete blood count was performed.

Pathological review and staging

Operative notes were reviewed to determine intraoperative suspicion of invasion, gross tumor extension into adjoining structures and completeness of resection. Pathology reports were obtained for all patients and the tumors were classified into Hyams histopathological grade. Staging was based on the surgical, radiological and pathological criteria as per TNM and Kadish Staging system [8, 16].

Treatment

Surgery, RT and CT was used in the treatment in different settings as per the stage and high risk features. Maximal safe resection (MSR) was the surgical approach with anterior craniofacial resection being done in patients with intracranial extension. Loco-regional RT was delivered in conventional 2 Gy per fraction as per the stage and extent of the disease. RT planning evolved with time and expertise and patients were planned with two-dimensional (2D), three-dimensional conformal (3DCRT) and intensity

modulated (IMRT) techniques. Chemotherapy regimen consisted of cisplatin and etoposide (PE regimen) administered on a 3-weekly interval.

Follow-up

The period between the first complaint and diagnosis was registered as symptom duration. Survival, recurrence and progression information were collected through chart review, patient or relative contact. Response evaluation was noted both clinically and radiologically and RECIST criteria were applied [17].

Statistical analysis

SPSS v 15 was used for statistical analysis. The Kaplan–Meier survival analysis was done for analyzing overall survival (OS) and duration of loco-regional control (LTC) [18].

Results

Patient characteristics

Patient characteristics are summarized in Table 1. Between November 2006 and November 2010, 15 patients of ENB were registered in our department. The median age of the patients was 35.0 years and ranges from 15 to 57 years. Ten patients (66.7 %) were males and five patients (33.3 %) were females. Most of them were in KPS 70 (seven patients). The median duration of symptoms was 5 months. Nasal obstruction was the most common presenting symptom manifesting in all patients followed by recurrent epistaxis, frontal headache, anosmia and impaired vision. Intracranial extension was seen in six patients (40 %) and two patients had neck node metastasis at presentation. Kadish C stage was the most common stage found in 12 patients (80.0 %) and the rest 3 patients (20 %) belonged to Kadish B stage. TNM classification included four patients (26.7 %) with T2, five (33.3 %) with T3 and six (40.0 %) with T4 tumors. Two patients (13.3 %) presented with N1 disease. On histopathological analysis, two patients (13.3 %) had Hyams grade I histology, two (13.3 %) had grade II, six had (40.0 %) grade III and five (33.3 %) had grade IV histology.

Treatment details (Table 2)

Treatment consisted of a combination of surgery (S), RT, and CT in 11 patients (73.3 %), S + RT in 3 (20.0 %) and RT + CT in 1 (6.7 %). Fourteen patients underwent surgery, out of which nine patients underwent total excision and five underwent subtotal excision, whereas one patient

Table 1 Patient characteristics

Total number of patients	15
Age (in years)	
Median	35.0
Range	15–57
Sex	
Male	10 (66.7 %)
Female	5 (33.3 %)
KPS	
60	2 (13.3 %)
70	7 (46.7 %)
80	2 (13.3 %)
90	4 (26.7 %)
Neck node	
Present	2 (13.3 %)
Absent	13 (86.7 %)
Intracranial extension	
Present	6 (40 %)
Absent	9 (60 %)
Kadish stage	
B	3 (20 %)
C	12 (80 %)
TNM stage	
T2	4 (26.7 %)
T3	5 (33.3 %)
T4	6 (40.0 %)
N0	13 (86.7 %)
N1	2 (13.3 %)
Hyam's grade	
I	2 (13.3 %)
II	2 (13.3 %)
III	6 (40.0 %)
IV	5 (33.3 %)

did not undergo surgical excision. Of the nine patients who underwent total excision, two patients had microscopically negative margins (R0) and seven patients had microscopically positive margins (R1). Five patients who had subtotal excision and one patient who did not undergo surgical excision were designated as R2 tumors. The surgical approaches varied from endoscopic resection to the craniofacial surgical resection, with the seven patients who underwent total excision were approached through craniofacial approach.

All patients received RT with a median dose of 54 Gy (range 50–60 Gy) in 2 Gy per fraction. RT was delivered using 2D RT in three patients (20.0 %), 3DCRT in eight (53.3 %) and IMRT in four (26.7 %). Planning treatment volume included the tumor bed in 13 patients (86.7 %), tumor bed and involved nodes in 2 patients (13.3 %). No cervical elective nodal irradiation was performed.

Table 2 Treatment details

Treatment approach	
Surgery + RT	3 (20.0 %)
Surgery + RT + CCT	11 (73.3 %)
RT + CCT	1 (6.7 %)
Surgery	
No	1 (6.7 %)
Subtotal excision	5 (33.3 %)
Total excision	9 (60.0 %)
Margins	
R0	2 (13.3 %)
R1	7 (46.7 %)
R2	6 (40.0 %)
RT	
Dose (median)	54.0 Gy
Dose (range)	50–60 Gy
RT neck	
Yes	2 (13.3 %)
No	13 (86.7 %)
RT modality	
2D	3 (20.0 %)
3DCRT	8 (53.3 %)
IMRT	4 (26.7 %)
CCT (PE regimen)	
Yes	12 (80.0 %)
No	3 (20.0 %)

CT was administered in 12 patients (80.0 %). CT regimen comprised cisplatin and etoposide (PE regimen). The CT was given in 3-weekly intervals with a median six number of cycles.

Treatment toxicity and compliance

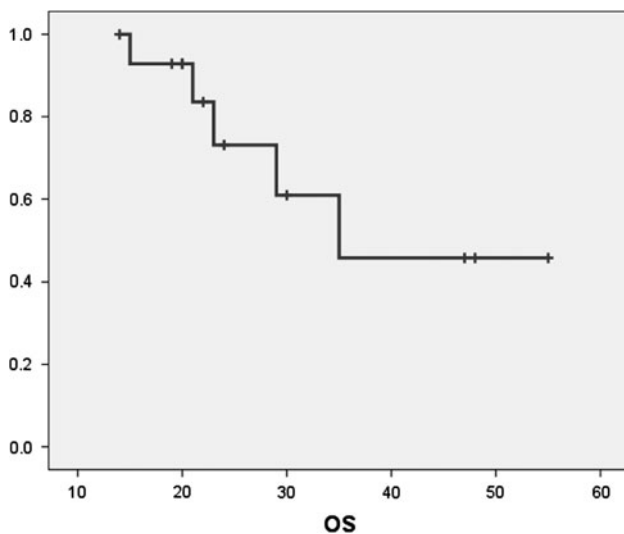
There were no surgical complications in form of post-operative deaths or wound complications. RT toxicity occurred in 12 patients (80 %) in form of grade 1–2 dermatitis and mucositis and there was no grade 3 or higher toxicity. CT toxicity was seen in seven patients in form of grade 1–2 hematological toxicity. All patients completed treatment with no significant toxicity or treatment interruption.

Clinical outcomes (Table 3)

After treatment completion, patients were assessed for response both clinically and radiologically. Ten patients (66.7 %) were asymptomatic, four patients (26.7 %) had significant improvement in symptoms and one patient (6.7 %) deteriorated. As per the RECIST criteria, eight patients (53.3 %) had CR, five patients (33.3 %) had PR,

Table 3 Response evaluation at treatment completion

Clinical response	
Asymptomatic	10 (66.7 %)
Improved	4 (26.7 %)
Deteriorated	1 (6.7 %)
Radiological response	
CR	8 (53.3 %)
PR	5 (33.3 %)
SD	1 (6.7 %)
PD	1 (6.7 %)

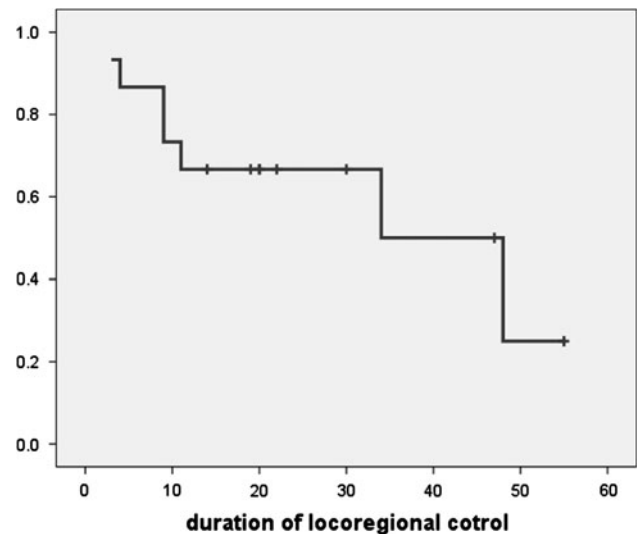
**Fig. 1** Kaplan-Meier Curve showing Overall Survival (OS)

while one had both SD and PD. Two patients developed distant metastases, one had bony metastases and the other had both bony and skin metastases. Median duration of follow-up was 23 months (range 14–55). Four-year OS of all patients was 45 % (Fig. 1) and 4-year LRC rates were 25 % (Fig. 2). The median OS was 35 months and the median duration of LRC was 34 months.

Discussion

Esthesioneuroblastoma is a rare and uncommon tumor arising from the olfactory epithelium in the upper nasal cavity [1, 2]. Data are based only on published series including small number of patients treated over a long period of time [5–7]. We herein report our institutional experience of 15 successive patients of ENB being treated from 2006 to 2010.

The majority of ENB is found with advanced disease in our series (80 % of patients in Kadish Stage C), which is in line with other series [5, 7, 9, 11]. The reason for this

**Fig. 2** Kaplan-Meier Curve showing Loco-regional Control (LRC)

advance stage of presentation is unspecific unrecognized initial symptoms (nasal obstruction, recurrent epistaxis, etc.).

The mainstay of the treatment is surgery. The current accepted practice is open or endoscopic craniofacial surgical resection [8, 9]. Fourteen of the 15 patients underwent primary surgery in our series. Nine patients (60 %) had total excision whereas five patients (33.3 %) had subtotal excision.

Adjuvant RT is indicated for Kadish Stage B and C, whereas Kadish A disease can be managed with surgery alone [8–10]. In our series, all the patients were locally advanced (12 patients had Kadish stage C and 3 patients had Kadish B stage) and received RT. The median RT dose delivered was 54 Gy (range 50–60 Gy). RT is delivered to the tumor bed and local extension with nodal irradiation reserved for involved nodes. Elective nodal irradiation is not practiced routinely. Two patients had nodal disease and received RT to involved nodal region in our series. With the evolution of newer RT techniques, sufficient conformal doses can be delivered with sparing of critical sensitive structures. Conventional 2D RT was planned in three patients (20 %), 3DCRT planning done in eight patients (53.3 %) and IMRT in four patients (26.7 %).

The role of CT is not well defined in literature [11–15]. Retrospective data suggests that patients with high grade, Kadish Stage C disease may benefit from adjuvant CT [12, 13]. Neoadjuvant CT can be used to reduce tumor burden to achieve R0/R1 resection [9, 19]. There is no standard CCT regimen in ENB, however, platinum-based regimens is reported to be efficient in advance stage tumors [15]. All of the patients in this series were locally advanced and 80 % of the patients received CCT with cisplatin and etoposide (PE regimen).

Local recurrence and/or distant metastases remain the main problem in the management of ENB [20]. Salvage treatment consists of surgery, surgery and postoperative RT, RT alone, palliative CCT, or supportive care depending on the type of relapse and initial treatment of the patient. Bachar et al. [11] reported a series of 39 patients of ENB treated in Princess Margaret Hospital in which local recurrence was documented in 12 patients (30.7 %), regional in 7 (17.9 %), and distant in 3 (7.7 %). In a meta-analysis by Dulguerov et al. [8], local, regional and distant recurrence rates were reported in 29, 16, and 17 %, respectively. In our series, seven patients had partial response or persistent disease (46.7 %) and two patients (13.3 %) had distant metastases.

The most important prognostic factors influencing the outcome reported in ENB are Hyams grade, positive lymph nodes, Kadish stage, extent of resection and postoperative RT with at least 54 Gy [21–23].

Most of the patients presents in locally advanced stage and thus the management of ENB is a paradigm of cooperation between clinicians, surgeons and pathologists from establishing diagnosis to organizing the therapeutic strategy. With new techniques and drugs, there is a significant improvement of therapeutic standard and ENB represent a model of therapeutic implementation and achievement in oncology. Novel strategies including combined CCT with RT and/or dose escalation with advanced RT techniques such as IMRT and proton therapy should be prospectively investigated.

Conflict of interest None.

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